Prognostic role of preoperative serum lipid levels in patients undergoing radical prostatectomy for clinically localized prostate cancer

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Abstract: BACKGROUND The prognostic role of preoperative serum lipid levels in patients undergoing radical prostatectomy (RP) for clinically localized prostate cancer (PCa) is unclear. The aim of the present study was to investigate preoperative serum lipid levels in patients with clinically localized PCa undergoing RP and their association with clinicopathological features and oncological outcome. METHODS Preoperative lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and statin use from consecutive patients with clinically localized PCa undergoing RP in a tertiary referral center between 2008 and 2015 were recorded and patients were followed prospectively. Logistic regression analysis was used to test the association between lipid levels and clinicopathological parameters. Lipid values were analyzed both as continuous and dichotomized variables. Univariable and multivariable Cox regression analyses were performed to identify predictors for recurrence-free survival (RFS). Recurrence was defined as rising and verified PSA levels >0.1 ng/ml. RESULTS Our cohort consisted of 371 men with a median age of 63 years (range 41-78 years) and a median preoperative PSA value of 6.79 ng/ml (0.43-81.4 ng/ml). Median follow-up was 28 months (1-64). No association was found between lipid levels and adverse pathological characteristics such as pT3, Gleason score 8, positive nodal status and positive surgical margins. Recurrence occurred in 49 patients (15.4%) at a median time of 18 months (2-51 month). Compared to low LDL cholesterol, high LDL cholesterol was associated with longer RFS in univariable analysis (continuous: Hazard Ratio (HR): 0.67, 95%-Confidence Interval (CI): 0.47-0.96, P = 0.03; 3 mM cut-point: HR: 0.44, 95%-CI: 0.24-0.79, P = 0.006). Neither levels of other lipids, nor statin use were associated with RFS. Preoperative LDL cholesterol remained an independent predictor for PCa recurrence in a multivariable model adjusted for age, preoperative PSA, statin use, tumor stage, Gleason score, nodal status and surgical margin status (continuous: HR: 0.66, 95%-CI: 0.44-0.99, P = 0.04; 3 mM cut-point: HR: 0.41, 95%-CI: 0.21-0.78, P = 0.007). CONCLUSIONS This is the first prospective study showing the potential adverse and independent prognostic role of low preoperative LDL cholesterol levels in patients with localized PCa undergoing RP. Prostate © 2017 Wiley Periodicals, Inc.

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Prognostic role of preoperative serum lipid levels in patients undergoing radical prostatectomy for clinically localized prostate cancer

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Running head: Serum lipids and biochemical recurrence

Conflicts of Interest

The authors of this article declare that they have nothing to disclose.

Abstract

Background: The prognostic role of preoperative serum lipid levels in patients undergoing radical prostatectomy (RP) for clinically localized prostate cancer (PCa) is unclear. The aim of the present study was to investigate preoperative serum lipid levels in patients with clinically localized PCa undergoing RP and their association with clinicopathological features and oncological outcome.

Methods: Preoperative lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and statin use from consecutive patients with clinically localized PCa undergoing RP in a tertiary referral center between 2008 and 2015 were recorded and patients were followed prospectively. Logistic regression analysis was used to test the association between lipid levels and clinicopathological parameters. Lipid values were analyzed both as continuous and dichotomized variables. Univariable and multivariable Cox regression analyses were performed to identify predictors for recurrence-free survival (RFS). Recurrence was defined as rising and verified PSA levels >0.1 ng/mL.

Results: Our cohort consisted of 371 men with a median age of 63 years (range 41-78 years) and a median preoperative PSA value of 6.79 ng/mL (0.43–81.4 ng/mL). Median follow-up was 28 months (1-64). No association was found between lipid levels and adverse pathological characteristics such as ≥pT3, Gleason score ≥8, positive nodal status and positive surgical margins. Recurrence occurred in 49 patients (15.4%) at a median time of 18 months (2-51 month). Compared to low LDL cholesterol, high LDL cholesterol was associated with longer RFS in univariable analysis (continuous: Hazard Ratio (HR): 0.67, 95%-Confidence Interval (CI): 0.47-0.96, p=0.03; 3 mM cut-point: HR: 0.44, 95%-CI: 0.24-0.79, p=0.006). Neither levels of other lipids, nor statin use were associated with RFS. Preoperative LDL cholesterol remained an independent predictor for PCa recurrence in a multivariable model adjusted for age, preoperative PSA, statin use, tumor stage, Gleason score, nodal status and surgical margin status (continuous: HR: 0.66, 95%-CI: 0.44-0.99, p=0.04; 3 mM cut-point: HR: 0.41, 95%-CI: 0.21-0.78, p=0.007).

Conclusions: This is the first prospective study showing the potential adverse and independent prognostic role of low preoperative LDL cholesterol levels in patients with localized PCa undergoing RP.

Key words

Prostate cancer, radical prostatectomy, biochemical recurrence, serum lipids

Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed cancers among men worldwide, with an estimated 1.1 million new cases and 0.3 million PCa-related deaths per year [1]. One well established treatment option for localized PCa with good long-term cancer control is radical prostatectomy (RP) [2]. Biochemical recurrence (BCR) after RP is often assumed to represent cancer and precede clinical progression. Even in specialized high-volume centers BCR rates after RP might reach up to 40% after 10 years [3].

The impact of serum lipid levels on the incidence of PCa and its natural course remains controversial [4,5]. A recent meta-analysis showed that total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol serum levels are unlikely to be associated with PCa risk [6]. However, the role of dyslipidemia in secondary prevention as a potential modifiable risk factor for PCa recurrence is even less clear. The association between complete preoperative serum lipid status and biochemical recurrence (BCR) after curative treatment for clinically localized PCa has only been investigated in a few studies, which have reported conflicting results [7–10]. For example, one study reported elevated serum triglycerides to be associated with increased risk of PCa recurrence [7], whereas another study found an association between hypertriglyceridemia and longer BCR-free survival [8]. Based on the conflicting results of studies in PCa patients, the association of preoperative lipid levels with BCR after curative treatment for localized PCa warrants further analysis. The aim of this study was to examine the association between the complete preoperative lipid status, clinicopathological features and BCR in men with clinically localized PCa.

Materials and Methods

Study design

Men with clinically localized PCa undergoing laparoscopic robotic assisted RP were prospectively included in this single-center cohort study (Prostate Cancer outcomes cohort study: ProCOC [11]). The study was approved by the Ethics Committee of Canton Zürich (protocol name: ProCOC: The Prostate Cancer Outcomes Cohort Study, protocol number: Ref. Nr. StV KEK-ZH-Nr. 06/08). The cohort consisted only of men with clinically localized PCa who were scheduled for RP at our tertiary referral center and gave informed consent. Patients were normally followed on a regular basis for every three months the first year and afterwards at least annually or on an individual basis depending on the disease course. A PSA value of 0.1 ng/ml or higher was defined as BCR. Patients were censored if lost to follow-up or event-free at their most recent clinic visit. Patients with a postoperative PSA persistence or without distinct follow-up data for the endpoint BCR were excluded from the analysis of BCR.

Pathologic analysis

All surgical specimens were processed according to standard histopathological procedures. At least one uropathologist assigned pathologic stage, tumor grade and node status. Surgical margins were considered positive if any neoplastic cells were in contact with the inked surface of the prostatectomy specimen. Tumor characteristics were obtained from pathology reports according to the WHO/ISUP 2016 classification.

Analysis of serum lipids

Preoperative serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) were assessed the day before surgery for all men according to the study protocol. Additionally, statin use at the time of surgery was recorded. The duration of

preoperative statin intake was not taken into account in this study. Blood analysis was performed by the hospital's Institute of Clinical Chemistry. Total cholesterol, HDL cholesterol and triglycerides were determined by enzymatic colorimetric tests in a modular analyzer (Cobas 8000, Roche Diagnostics GmbH, Mannheim, D). *Friedewald´s formula* (*LDL cholesterol = Total cholesterol – [HDL cholesterol + { triglycerides / 5 }]*) was used to calculate serum LDL cholesterol values [12]. However, this formula is not valid for triglyceride levels >4.5 mmol/L (mM) and patients with levels above this threshold were thus excluded from any analysis using LDL cholesterol as a variable.

Statistical analysis

Univariable logistic regression analysis was used to analyse the association between serum lipid levels, statin use and clinicopathological tumor characteristics. Clinicopathological study outcomes were extraprostatic disease (≥pT3), high-risk disease (Gleason Score ≥8), positive nodal status (pN1) and positive surgical margins (PSM).

Serum lipid levels in the regression analysis were analyzed as continuous and as binary variables. Cut-points were selected according to the reference values of the hospital's Institute of Clinical Chemistry that are based on internationally accepted threshold values (total cholesterol: 5 mM, LDL cholesterol: 3 mM, HDL cholesterol: 1 mM, triglycerides: 1.7 mM) [13].

Univariable and multivariable Cox regression models addressed the association of serum lipid levels with BCR after RP. Adjustments were made for age, preoperative PSA, statin use, tumor stage, Gleason score, nodal status and surgical margin status. We constructed Cox regression models for each single adjustment factor and one model containing all adjustment factors.

Cut-point analysis was conducted for independently prognostic serum lipid values to detect other significant dichotomization cut-points (0.5 mM increments). Multiple comparisons were

handled by adjusting the p-values with the false-discovery rate (FDR) approach described by *Benjamini & Hochberg* [14]. Finally, Kaplan-Meier survival plots with their corresponding log-rank tests were drawn for all significant cut-points that were found in the cut-point analysis.

R programming language and software environment version 3.1.3 (R Foundation for Statistical Computing, Vienna, A) was used to perform all statistical analyses. All p-values were two-sided with p-values <0.05 considered statistically significant.

Results

Between 2008 and 2015, a total of 371 consecutive PCa patients before RP were included. The clinical and pathological characteristics, preoperative serum lipid levels and statin use are summarized in Table 1. A total of 108 (29.2%) men had extraprostatic disease and 79 (21.4%) had high-risk disease (Gleason score ≥8). Furthermore, 25 (6.7%) men were diagnosed with lymph node metastasis. Pelvic lymphadenectomy was performed in 277 (74.7%) men. Median preoperative serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) are also presented in Table 1. LDL cholesterol was non-calculable in five patients (1.3%) due to high cholesterol levels (>4.5 mM). These patients were excluded from all analyses, which used LDL cholesterol as a variable. A total of 61 (16.4%) men were statin users at the time of surgery. A total of 52 patients (14%) were excluded from the analysis of time to BCR due to postoperative PSA persistence (*n*=17) or unavailable follow-up data regarding BCR (*n*=35) after RP. Median follow-up time for the remaining 319 men was 28 months (range 1-64). BCR occurred in 49 patients (15.4%) after a median time of 18 months (2-51).

Univariable logistic regression analysis (Table 2) revealed a significant association between triglycerides (continuous) and high-risk disease (OR: 1.32; 95%-CI: 1.03-1.69; p=0.03). However, the association between triglycerides and high-risk disease could not be confirmed when triglycerides were used as a dichotomized variable (OR: 1.05; 95%-CI: 0.63-1.75; p=0.86). All other serum lipid levels (continuous and dichotomized) did not reveal any significant association with pathological tumor characteristics (Table 2). Among all pathological parameters, statin use only showed a positive association with PSM (OR: 1.94; 95%-CI: 1.12-3.39; p=0.02). In an additional univariable logistic regression analysis, preoperative serum lipid levels and statin use were not associated with high preoperative PSA values (≥10 ng/ml) (Table S1).

For prognostic association of serum lipid levels and statin use uni- and multivariable Cox regression analyses were performed. Among all preoperative lipid values, only high LDL (continuous and 3 mM cut-point) cholesterol values were significantly associated with longer recurrence free survival (RFS) compared to low LDL values in univariable analysis (continuous: HR: 0.67, 95%-CI: 0.47-0.96, p=0.03; 3 mM cut-point: HR: 0.44, 95%-CI: 0.24-0.79, p=0.006). Additionally, all clinicopathological study outcomes (stage ≥pT3, Gleason score ≥8, pN1 and PSM) were highly associated with a shorter RFS (for all p<0.001) in univariable analyses (Table 3). Statin use was not associated with RFS (HR: 1.75, 95%-CI: 0.91-3.37, p=0.09).

Regression parameters from multivariable models evaluating the independent prognostic utility of LDL cholesterol (continuous and 3 mM cut-point) are presented in Table 4. LDL cholesterol remained an independent prognostic factor in a multivariable models adjusting for age, PSA, extraprostatic disease, high-risk disease, positive nodal status, PSM and statin use.

Table S2 shows cut-point testing for LDL cholesterol (1.5 to 5 mM). After correction for multiple comparisons, 3.5 mM was another cut-point (besides 3.0 mM) that could predict time to BCR (HR: 0.38; 95%-CI: 0.19-0.77; p=0.01; FDR-adjusted p-value: 0.03). Finally, Kaplan-Meier analysis in regard to BCR for the two LDL cholesterol cut-points (Figure 1: 3.0 mM, Figure 2: 3.5 mM) confirmed that the low LDL cholesterol subgroups were significantly associated with shorter time to BCR (p=0.005 for both cut-points).

Discussion

Altered lipid metabolism has been acknowledged as a hallmark of many cancers including PCa [15,16]. Cancer cells exhibit increased lipid metabolism for energy generation and intracellular signaling, both of which are important for maintaining tumor cell survival [17]. Thus, there is a biological rationale for the investigation of dyslipidemia and lipid levels in cancer patients. Furthermore, epidemiologic studies have suggested that systemic metabolic disorders might be involved in PCa development and progression [18]. In this study we evaluated the prognostic role of preoperative serum lipid levels after a median follow-up of 28 months in 371 patients. Low LDL cholesterol remained an independent predictor for shorter RFS after RP for localized PCa. Other preoperative serum lipid serum levels (total cholesterol, HDL cholesterol and triglycerides) and statin use showed no significant association with the clinical course after RP in this cohort.

The main strength of this work is the prospective comprehensive evaluation of the complete preoperative lipid status consisting of the main serum lipid parameters and statin intake before RP. Only few studies in the past have evaluated the association of the complete preoperative serum lipid status and RFS after curative treatment for localized PCa. Regarding the prognostic role of LDL cholesterol conflicting results have been reported [7–10].

Two studies did not find any association between preoperative LDL cholesterol and outcome after RP for localized PCa. However, only one study [8] is comparable to ours. The cohort of the second study by *Allot et al.* [7] is characterized by almost 40% Gleason 6 cancer patients (compared to 13% in our cohort). Moreover, no information about the time point of blood sampling before surgery is available for this study. Two further studies reported pretreatment high LDL cholesterol levels to be associated with PCa recurrence, which contradicts our results [9,10]. Most patients in these two studies were treated with percutaneous radiotherapy and are thus not directly comparable to our work. Additionally, both studies have again reported a much higher amount of low risk PCa patients (between 44% up to 60% Gleason 6

cancer) compared to our study. Finally, only a small subset of the entire cohort could be investigated for the complete pretreatment lipid levels (including LDL cholesterol) in one of the two studies [9]. In conclusion, different results have been reported regarding LDL cholesterol and its association with outcome after treatment of PCa. Heterogeneous cohorts with different populations and different therapies limit the comparison between the mentioned studies. To the best of our knowledge, our study is the first reporting preoperative low LDL cholesterol levels to be associated with PCa recurrence in men with localized PCa undergoing RP.

The role of low serum cholesterol on carcinogenesis is a hot topic in epidemiologic research, especially due to the high prevalence of cardiovascular morbidity and the resulting prescription of lipid-lowering agents such as statins [19–25].

One might explain the results of our investigation by the following hypothesis: Patients with preoperatively low LDL cholesterol levels may represent a group with higher and more aggressive tumor burden, which has the ability to alter the body´s lipid metabolism leading to lower LDL cholesterol values and a higher risk for BCR. The essential question – as asked in a comprehensive Mendelian randomization study of *Benn et al.* [26] – is if the often independent association between low serum lipid levels and adverse oncologic outcomes is caused by a possible carcinogenic effect of low serum lipid levels or if we see a reverse causality, in which a preclinical malignancy alters the serum lipid metabolism. The study, which included over 10 000 participants, concludes that low LDL cholesterol is probably secondary to preclinical cancer and that a causal relationship between serum lipid values and carcinogenesis is unlikely. *Gilbert et al.* demonstrated an inverse relationship between tumor mass of hematological cancers and serum cholesterol [27].Possible cell-biologic explanations for the reduction of LDL cholesterol in oncologic patients are the overutilization of serum lipids by cancer cells or the secretion of a humoral factor (by cancer cells) which stimulates normal cells to utilize LDL cholesterol [28–30]. A recent study has demonstrated that PCa

cells require cholesterol for cell growth *in vitro*, thus it is reasonable to assume that faster growing tumors would consume more circulating LDL cholesterol [31]. In summary, the adverse role of low LDL cholesterol may be rather interpreted as a cause of cancer and may thus not represent a modifiable risk factor in preventing risk of PCa recurrence. As only preoperative serum lipid values were available for analysis, the dynamic changes of these parameters during the postoperative follow-up period, which might have yielded additional interesting results, were not included in this study, but should be included in future study protocols.

Studies from basic and translational research suggest a role for statins in PCa development or recurrence by several mechanisms [32]. In our study, statin use was not associated with PCa recurrence after RP. Conflicting results have been reported regarding statin use and PCa recurrence after curative treatment for localized disease. In line with our work, two relatively new meta-analyses that included patients undergoing RP or curative radiation therapy could not detect a significant association between statin use and PCa recurrence after RP [33,34].

Our study has limitations: Firstly, the relatively short follow-up time, which led to a limited number of events. Secondly, only BCR and not PCa specific mortality was available as an oncological outcome parameter. BCR is a suboptimal oncological endpoint for PCa due to its rather limited ability to predict cancer-specific survival in PCa [35]. However, a shorter RFS is a surrogate marker for worse outcome in PCa after curative treatment [36,37]. Thirdly, other possible covariates/confounders of serum lipid status such as BMI or smoking status were not available for this study. Finally, the duration of preoperative statin intake was not controlled. However, the prediction of a shorter RFS by low LDL cholesterol was independent from statin intake in multivariable analyses. Our work provides a comprehensive blood analysis of all preoperative lipid serum levels in a consecutive series of PCa patients undergoing RP.

Conclusions

This is the first study showing the potential prognostic role of low preoperative LDL cholesterol levels in a prospective cohort of patients with localized PCa undergoing RP. If long-term outcomes confirm our findings, preoperative low LDL cholesterol values might be used to categorize patients with localized PCa in a high-risk group for disease recurrence.

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Figure legends

Figure 1: Kaplan-Meier analysis and the corresponding log-rank test comparing time to biochemical recurrence between patients with low and high LDL cholesterol levels (3.0 mM cut-point).

Figure 2: Kaplan-Meier analysis and the corresponding log-rank test comparing time to biochemical recurrence between patients with low and high LDL cholesterol levels (3.5 mM cut-point).